

**REMARKS**

Reconsideration is requested.

The specification has been amended to include a cross-reference to the parent application. The applicants submit that the time periods for making such an Amendment, as described in Rule 78(a)(5)(ii) do not apply, pursuant to the exception provided in Rule 78(a)(5)(ii)(B). The Examiner is requested to advise the undersigned however if anything further is required in this regard.

The Patent Office has acknowledged receipt of the priority document from the International Bureau. See, Notification of Acceptance dated June 28, 2001. The Examiner is requested to confirm the same by indication on page 1 of the next Office Action or Notice of Allowance.

The Section 102 rejection of claims 1, 5 and 7 over Moriuchi *et al.* (J. Virol., 1993, Vol. 67, pp. 2739-2746) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

Independent Claim 1 is directed to a process for preparing a pharmaceutical composition comprising the step of formulating the mutant HSV with a pharmaceutically acceptable carrier or diluent. The applicants submit that Moriuchi *et al.* teaches that the yield of HSV-1 *in1814* may be increased by growing the virus on cells expressing VZV ORF10. Moriuchi *et al.* does not however teach that HSV-1 *in1814* may then be harvested and purified. Accordingly, Moriuchi *et al.* does not disclose HSV-1 *in1814* produced using a VZV ORF cell line contained in a pharmaceutically acceptable carrier or diluent. The Examiner's reliance on an alleged inherent teaching of the cited art at

page 3 of the Office Action dated July 29, 2003 (Paper No. 19) is not supported by any evidence of record.

Moreover, the paragraph referred to by the Examiner (page 2744 line 9 first column to line 6 second column) does not relate in any way to the *in1814* mutant HSV-1 grown on VZV ORF10 expressing cells. This paragraph is understood by the applicants to describe the production of infective wild-type HSV-1 virus following the introduction of wild-type HSV-1 DNA into cells (see page 2743 last two lines to page 2744 lines 1 to 8).

The experiment described at page 2744 shows that production of infective wild-type HSV-1 virus following the introduction of wild type HSV-1 DNA into cells expressing VZV ORF is enhanced compared to production following transfection of control cells. The HSV-1 DNA used in these experiments does not comprise a mutation in the VP16 gene. Accordingly, the virus produced by the VZV ORF10 expressing cells is wild-type HSV-1 that expresses a wild-type VP16 gene. It is this wild-type virus that was harvested and cultured as described in Moriuchi *et al.* at page 2744. Moriuchi *et al.* does not disclose a method comprising the steps of propagating a herpes simplex virus having a mutation in its endogenous VP16 gene using a VZV ORF expressing cell line, isolating the herpes simplex virus and formulating the isolated herpes simplex virus in a pharmaceutically acceptable carrier or diluent. The cited reference therefore fails to teach, literally or inherently, each and every aspect of the presently claimed invention.

Claims 1, 5 and 7 are submitted to be patentable over Moriuchi and withdrawal of the Section 102 rejection over the same is requested.

The Section 103 rejection of claims 1, 3-5, 7-10, 27 and 28-58 over Speck *et al.* (WO96/04395 A1), Moriuchi *et al.* and Purewall *et al.* (Virology 1994, vol 198, pp. 385-

389) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

Speck *et al.* teaches that the VP16 mutation in the HSV should be one that allows growth in the presence of hexamethylene bisacetamide (HMBA) (page 4 lines 3 to 6) and teaches that the mutant virus should be grown in the presence of HMBA (page 27 lines 25 to 35). Speck *et al.* also addresses the issue of growing mutant viruses on a complementing cell line (see page 6 line 21 to page 7 line 14) giving IE0, IE4, IE27 and gH as examples of mutated genes that may be complemented in a cell line. However, the applicants submit that Speck *et al.* does not teach or suggest that a mutation in the VP16 gene may be complemented using a cell line. In fact, Speck *et al.* is believed to teach away from using a cell line to complement the mutated VP16 gene stating that "*it is preferred, however, not to complement a mutation in the VP16 gene in the complementing cell line, since the effect of the mutation in this particular gene is considered to be obtained where the mutant gene product forms part of the virion*" (see page 7 lines 8 to 12). Hence, one of ordinary skill in the art reading Speck *et al.* may have appreciated that, in theory, VP16 expressed in a cell line could have been used to complement a mutation in the VP16 gene of the HSV but that such complementation would not have been desirable where the mutant virus was intended for use as a pharmaceutical vaccine or vector.

Moriuchi *et al.* teaches that VZV ORF10 could have been used to increase the yield of the HSV-1 *in1814* mutant. One of ordinary skill in the art may, therefore, have appreciated that VZV ORF10 can complement an HSV VP16 mutation. However, Moriuchi *et al.* is not at all concerned with the production of safe mutant herpes viruses

suitable for use as pharmaceutical vectors or vaccines. Accordingly, Moriuchi *et al.* provided no teaching or suggestion to one of ordinary skill in the art as to whether expression of the VZV ORF10 gene in a complementing cell line may or may not have been a suitable alternative to HMBA in the propagation of HSV vectors or vaccines comprising a mutation in the VP16 gene.

Similarly, although Purewall *et al.* teaches that EHV-1 and EHV-4 homologs of VP16 strongly transactivate HSV-1 IE genes, this document is not concerned with the production of safe mutant herpes viruses for use as vaccines or vectors. Accordingly, Purewall *et al.* did not provide the skilled person with any guidance as to whether or not a VP16 mutant HSV for use as a pharmaceutical could have been grown in the absence of HMBA on a complementing cell expressing a EHV-1 or EHV-4 homolog of VP16.

Thus, neither Moriuchi *et al.* or Purewall *et al.* taught or suggested that use of a VP16 homolog in a complementing cell line is a safe alternative to using HMBA to promote growth of a VP16 mutant HSV. Neither document would have led a person of ordinary skill in the art away from the teaching in Speck *et al.* that a mutation in the VP16 gene of HSV should not be complemented in a cell line used for the production of vectors or vaccines for pharmaceutical use, but compensated for using HMBA. A person of ordinary skill in the art at the time that the invention was made would not, therefore, have been motivated to propagate a VP16 mutated HSV for use in a pharmaceutical formulation using a complementing cell line expressing a VP16 homolog. Accordingly, the presently claimed invention would not have been obvious over Speck *et al.* in view of Moriuchi *et al.* and Purewall *et al.* Withdrawal of the Section 103 rejection is requested.


COFFIN et al.  
Appl. No. 09/762,098  
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Having fully responded to all of the pending rejections and objections contained in Paper No. 19, Applicants submit that the claims are in condition for allowance and earnestly solicit an early notice to that effect.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: \_\_\_\_\_



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